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Cefepime Therapy for Monomicrobial *Enterobacter cloacae* Bacteremia: Unfavorable Outcomes in Patients Infected by Cefepime-Susceptible Dose-Dependent Isolates

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A new category of cefepime susceptibility, susceptible dose dependent (SDD), for *Enterobacteriaceae*, has been suggested to maximize its clinical use. However, clinical evidence supporting such a therapeutic strategy is limited. A retrospective study of 305 adults with monomicrobial *Enterobacter cloacae* bacteremia at a medical center from 2008 to 2012 was conducted. The patients definitively treated with *in vitro* active cefepime (cases) were compared with those treated with a carbapenem (controls) to assess therapeutic effectiveness. The 30-day crude mortality rate is the primary endpoint, and clinical prognostic factors are assessed. Of 144 patients receiving definitive cefepime or carbapenem therapy, there were no significant differences in terms of age, sex, comorbidity, source of bacteremia, disease severity, or 30-day mortality (26.4% versus 22.2%; $P = 0.7$) among those treated with cefepime ($n = 72$) or a carbapenem ($n = 72$). In the multivariate analysis, the presence of critical illness, rapidly fatal underlying disease, extended-spectrum beta-lactamase (ESBL) producers, and cefepime-SDD (cefepime MIC, 4 to 8 μg/ml) isolates was independently associated with 30-day mortality. Moreover, those infected by cefepime-SDD isolates with definitive cefepime therapy had a higher mortality rate than those treated with a carbapenem (5/7 [71.4%], versus 2/11 [18.2%]; $P = 0.045$). Cefepime is one of the therapeutic alternatives for cefepime-susceptible *E. cloacae* bacteremia but is inefficient for cases of cefepime-SDD *E. cloacae* bacteremia compared with carbapenem therapy.

Enterobacter cloacae is an increasingly important pathogen and causes a wide variety of serious community- and health care-associated infections (1–3). Rapid emergence of multidrug resistance has been documented in individual patients during therapy and in populations with strong selective pressure from antimicrobial agents (3–5). *E. cloacae* isolates are traditionally characterized by chromosomally encoded AmpC beta-lactamases and have the ability to develop resistance upon exposure to broad-spectrum cephalosporins (6). Moreover, a growing number of *E. cloacae* strains with extended-spectrum beta-lactamases (ESBLs) have been observed worldwide (5, 7). Therapeutic options for patients infected by multidrug-resistant strains have become severely limited.

Cefepime, with greater stability against ESBL and AmpC enzymes than other extended-spectrum cephalosporins (8), is considered a treatment option for infections caused by this organism (1, 9, 10). *In vitro* data suggest that cefepime, unlike other cephalosporins, maintains antibacterial activity against AmpC-producing isolates (11). Therefore, invasive infections caused by AmpC beta-lactamase-producing organisms, such as *E. cloacae*, are often treated with cefepime or a carbapenem.

Owing to a better understanding of the pharmacokinetic/pharmacodynamic (PK/PD) determinants and resistance mechanisms, more emphasis on drug target attainment for beta-lactam antibiotics than on the identification of resistance mechanisms has been proposed (12). The Clinical and Laboratory Standards Institute (CLSI) (13) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (14) revised the susceptibility breakpoints for cephalosporins and omitted the requirement for ESBL phenotype detection. Physicians are reminded to exercise caution, as many clinical microbiology laboratories no longer routinely report the presence of ESBL phenotypes, which causes confusion in selecting appropriate antibiotics (15). Also, CLSI introduced a new susceptibility category for cefepime, i.e., susceptible dose dependent (SDD; MIC, 4 to 8 μg/ml) (16). Higher cefepime doses are recommended for severe infections due to the *Enterobacteriaceae* isolates with a MIC of 4 μg/ml (2 g every 12 h or 1 to 2 g every 8 h) or 8 μg/ml (2 g every 8 h). However, clinical evidence to support this approach is limited (15). Our objective is to analyze clinical outcomes of adults with bloodstream infections due to cefepime-SDD *E. cloacae* definitively treated with cefepime or a carbapenem in comparison with those of cefepime-susceptible *E. cloacae* bacteremia treated with cefepime.

MATERIALS AND METHODS

Study population and data collection. We reviewed the microbiology database at National Cheng Kung University Hospital (NCKUH) in southern Taiwan between May 2008 and August 2012 for cases of *E. cloacae* bacteremia. If a patient experienced more than one bacteremic episode, only the first episode was included. The study was approved by the NCKUH Institutional Review Board (ER-100-182). The isolates with ESBL production have been previously described (7). Included were adult

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patients (age, ≥18 years) fulfilling all of the following criteria: (i) clinically significant bacteremia with compatible sepsis syndrome and (ii) parenteral therapy with cefepime or a carbapenem for more than 48 h before the end of antimicrobial therapy or death (17) and adequate doses as recommended by the CLSI, according to the susceptibility categories (16). Patients with polymicrobial bacteremia were excluded.

The empirical therapy group included the patients who received cefepime or carbapenem monotherapy, of which the first dose was administered during the first 24 h after blood cultures had been taken. Antimicrobial therapy administered within 5 days after bacteremia onset was regarded as empirical therapy and administered afterward as definitive therapy. The definitive therapy group consisted of those receiving definitive cefepime or carbapenem monotherapy if the causative isolate was *in vitro* susceptible to the prescribed drug according to the current criteria of CLSI (16). The clinical choice of antibiotics was at the discretion of the attending physician. Included patients would receive the following doses or adjusted equivalents in the cases of renal insufficiency: ertapenem (1 g every 24 h), imipenem (0.5 g every 6 h), meropenem (1 g every 8 h), or cefepime (1 to 2 g every 8 to 12 h; 2 to 6 g/day). The prescriptions of carbapenems and cefepime would be approved by infectious disease specialists and pharmacists for their indications and dosages in the study hospital.

***In vitro* susceptibility tests and extended-spectrum beta-lactamase detection.** Clinical isolates were screened for ESBL production among third-generation-cephalosporin-nonsusceptible isolates. The ESBL phenotype was determined by the Etest ESBL strip (AB Biodisk, Solna, Sweden) and confirmed by PCR and sequence analyses (7). The MICs of carbapenems and cefepime were determined by the agar dilution method, and the interpretation followed the breakpoints recently recommended by CLSI in 2014 (16).

Clinical evaluation and outcomes. Clinical information was retrieved from medical charts and collected in a case record form. Bacteremia was defined as the isolation of the organisms in at least one blood culture with compatible clinical features. Patients receiving cefepime or carbapenem therapy for more than 48 h with adequate dosage were included for assessment of outcome. The primary outcome was the crude 30-day mortality rate. Immunosuppression was referred to the receipt of corticosteroid (at least 10 mg or an equivalent dosage daily) for more than 2 weeks or of antineoplastic chemotherapy or antirejection medication within 4 weeks before the onset of bacteremia. The severity of underlying medical illness was stratified as being fatal, ultimately fatal, or nonfatal (18). The severity of bacteremia was graded on the day of bacteremia onset using the Pitt bacteremia score (19). Clinical failure was defined as follows: for at least 5 days, initial antimicrobial therapy failed to resolve sepsis symptoms or signs, or a fatal outcome ensued. The detection of *E. cloacae* bacteremia during antimicrobial therapy for at least 72 h was regarded as microbiological failure.

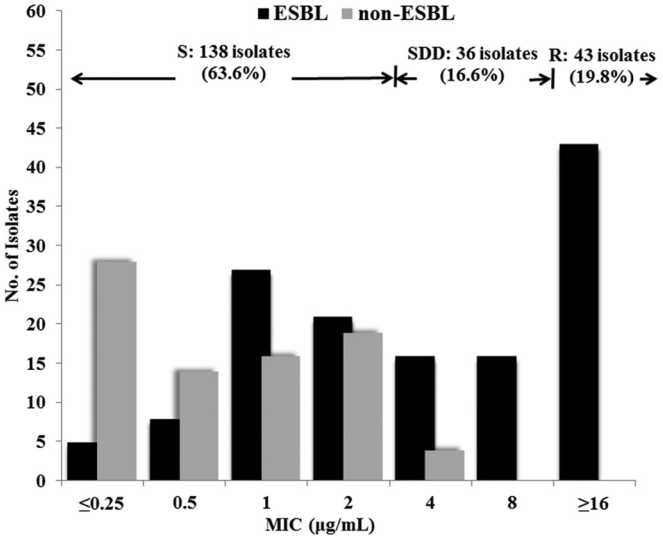

FIG 1 Distribution of cefepime MICs of 217 *Enterobacter cloacae* blood isolates, with or without extended-spectrum beta-lactamase (ESBL) production. S, susceptible; SDD, susceptible dose dependent; R, resistant.

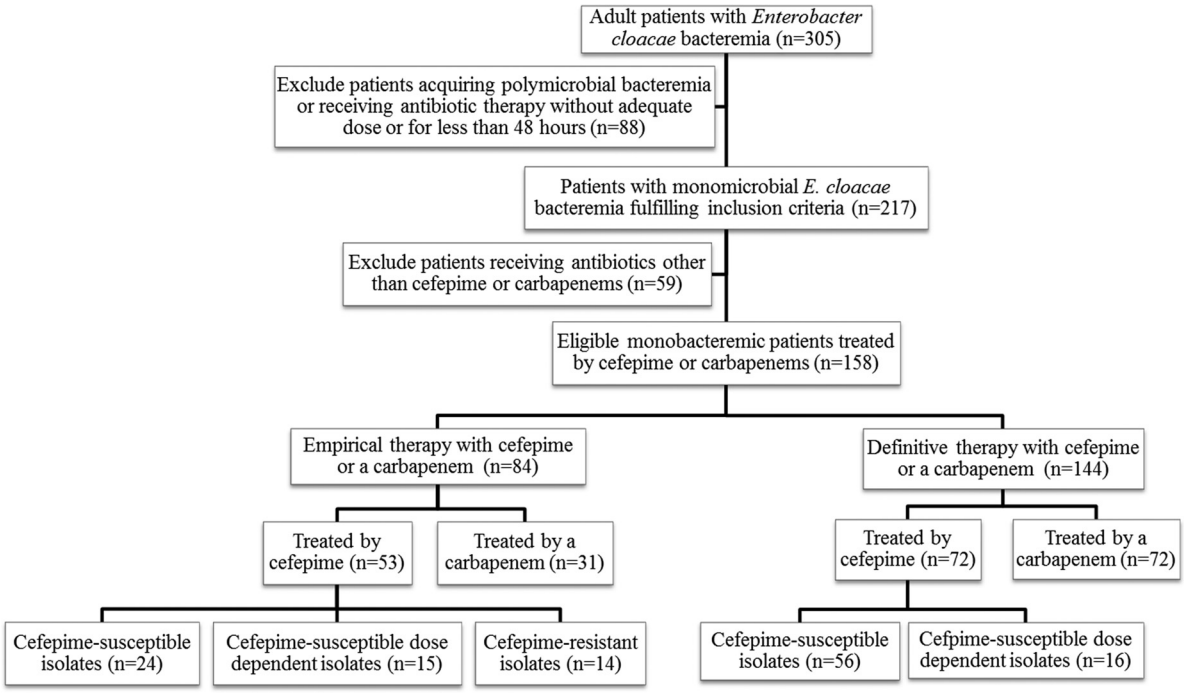

FIG 2 Study flow of the case numbers of included and excluded patients with monomicrobial *Enterobacter cloacae* bacteremia.

Statistical analysis. Data were analyzed by the SPSS software for Windows, version 18.0. Continuous variables were expressed as mean values ± standard deviations (SDs) and compared by the Mann-Whitney U test or Student *t* test. Categorical variables were expressed as percentages of total numbers of patients and compared by the Fisher exact test or χ^2 test, as appropriate. Independent predictors for mortality were identified by means of logistic regression analysis. Variables with a *P* value of 0.1 or less, as determined by the univariate analysis, were included in a multiple conditional logistic regression analysis. We compared Kaplan-Meier survival curves with the log rank test. A Cox proportional hazard model was applied for the survival analysis, adjusted for confounding variables. A *P* value less than 0.05 was considered statistically significant, and all tests were two-tailed.

RESULTS

In the study period, overall 305 adults experienced *E. cloacae* bacteremia, and there were 272 with *E. cloacae* monomicrobial bacteremia. Of these, 217 (79.8%) patients met the inclusion criteria for the analyses of microbiological and clinical outcome. Cefepime MICs of 217 *E. cloacae* isolates ranged from ≤0.25 to ≥16 μg/ml, and $MIC_{50/90}$ was 2/≥16 μg/ml. According to the

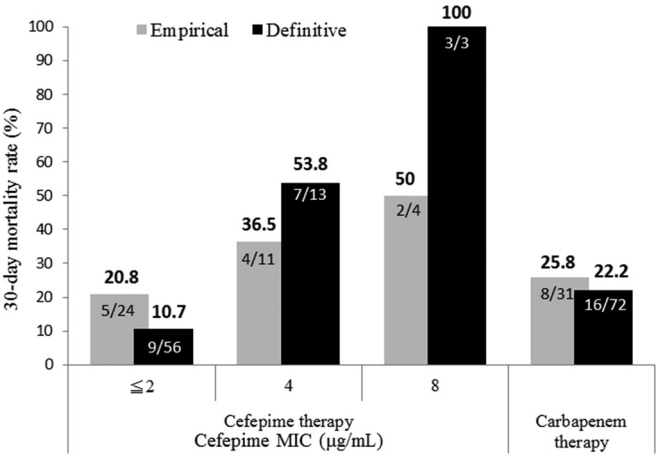

FIG 3 Clinical outcome (30-day mortality rates) of the cases of bloodstream infections caused by *Enterobacter cloacae* isolates empirically and definitively treated with cefepime or a carbapenem. The prescribed drugs and dosages are currently regarded as being appropriate. Those with cefepime therapy are further categorized by cefepime MIC of the bacteremic isolates. The numbers in the bars indicate the numbers of fatal/total cases.

TABLE 1 Characteristics of 144 patients with *Enterobacter cloacae* bacteremia definitively treated with cefepime or carbapenem[a]

Characteristic	Carbapenem group (*n* = 72)	Cefepime group (*n* = 72)	*P* value
Age, median (IQR), yr	75 (57–78)	66 (52–76)	0.27
Gender, male	43 (59.7)	42 (58.3)	1.00
Route of acquisition			0.75
Hospital onset	68 (94.4)	66 (91.7)	
Community onset	4 (5.6)	6 (8.3)	
Length of hospital stay before bacteremia, median (IQR), days	25 (14–52)	15 (6–36)	0.10
Comorbidity			
Diabetes mellitus	30 (41.7)	25 (34.7)	0.49
Chronic kidney disease	22 (30.6)	15 (20.8)	0.25
Malignancy	21 (29.2)	23 (31.9)	0.86
Neutropenia	2 (2.8)	11 (15.3)	0.02
Liver cirrhosis	5 (6.9)	8 (11.1)	0.56
None	6 (8.3)	10 (13.9)	0.43
ESBL producer	53 (73.6)	42 (58.3)	0.04
Cefotaxime nonsusceptible	55 (76.4)	40 (55.6)	0.01
Severity of underlying disease (McCabe classification)			0.35
Rapidly fatal	8 (11.1)	13 (18.1)	
None or nonrapidly fatal	64 (88.9)	59 (81.9)	
Pitt bacteremia score of ≥4	28 (38.9)	28 (38.9)	1.00
Source of bacteremia			
Vascular catheter-related infection	23 (31.9)	30 (41.7)	0.30
Primary bacteremia	23 (31.9)	22 (30.6)	1.00
Intra-abdominal infection	5 (6.9)	6 (8.3)	1.00
Pneumonia	9 (12.5)	4 (5.6)	0.24
Skin and soft tissue infection	3 (4.2)	5 (6.9)	0.72
Urinary tract infection	6 (8.3)	5 (6.9)	1.00
Hospital stay of survivors after bacteremia, median (IQR), days	28 (18–53)	21 (16–38)	0.13
Clinical failure	30 (41.7)	27 (37.5)	0.73
Microbiological failure	7 (9.7)	13 (18.1)	0.23
Sepsis-related mortality	8 (11.1)	12 (16.7)	0.47
30-day mortality	16 (22.2)	19 (26.4)	0.70
Crude mortality	31 (43.1)	26 (36.1)	0.50

[a] Data are given as numbers (percentages), unless otherwise specified.

TABLE 2 Multivariate logistic regression analysis of the variables associated with 30-day mortality among 72 patients with monomicrobial *Enterobacter cloacae* bacteremia definitively treated with cefepime[a]

Variable	No. (%) (except for age)		Univariate analysis		Multivariate analysis	
	Survivors ($n = 53$)	Nonsurvivors ($n = 19$)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, median (IQR), yr	66 (51–77)	68 (58–73)	—	0.70		
Male gender	32 (60.4)	10 (52.6)	0.73 (0.25–2.10)	0.60		
Diabetes mellitus	20 (37.7)	5 (26.3)	1.43 (0.18–1.88)	0.42		
Chronic kidney disease	11 (20.8)	4 (21.1)	1.02 (0.28–3.69)	1.00		
Malignancy	14 (26.4)	9 (47.4)	2.51 (0.85–7.44)	0.15		
Liver cirrhosis	5 (9.4)	3 (15.8)	1.8 (0.39–8.39)	0.43		
Pitt bacteremia score of ≥4	15 (28.3)	13 (68.4)	5.49 (1.76–17.11)	0.005	4.40 (1.02–18.89)	0.04
Rapidly fatal underlying disease	6 (11.3)	7 (36.8)	4.57 (1.29–19.13)	0.03	11.27 (1.72–73.94)	0.01
High-dose cefepime regimen[b]	22 (41.5)	6 (31.5)	0.65 (0.21–1.97)	0.59	0.39 (0.06–2.57)	0.33
Cefepime-SDD isolate	6 (11.3)	10 (52.6)	8.7 (2.52–30.02)	0.001	18.04 (2.66–122.18)	0.003
ESBL producer	24 (45.3)	16 (84.2)	6.44 (1.68–24.77)	0.006	12.34 (2.10–72.56)	0.005

[a] Abbreviations: —, not available; OR, odds ratio; CI, confidence interval; IQR, interquartile range; SDD, susceptible dose dependent; ESBL, extended-spectrum beta-lactamase.
[b] Cefepime at 2 g every 8 h.

updated criteria of CLSI (16), 43 (19.8%) isolates were classified as resistant (MIC, ≥16 μg/ml), 36 (16.6%) were classified as SDD (MIC, 4 to 8 μg/ml), and 138 (63.6%) were classified as susceptible (MIC, ≤2 μg/ml) to cefepime (Fig. 1). Of these, 136 (62.7%) ESBL-producing isolates had higher cefepime MICs (median, 4 μg/ml; interquartile range [IQR], 1 to ≥16 μg/ml) than did the isolates without ESBL (median, 0.5 μg/ml; IQR, ≤0.25 to 2 μg/ml; $P < 0.001$, linear-by-linear association). Moreover, ESBL production was more common in cefepime-SDD isolates than cefepime-susceptible isolates (88.9% [32/36] versus 44.2% [61/138]; $P < 0.001$).

Empirical therapy. According to the study criteria, there were 84 patients in the empirical therapy group and 144 in the definitive therapy group (Fig. 2). In the former, 53 patients were empirically treated with cefepime and 31 were treated with a carbapenem (i.e., 3 ertapenem, 12 meropenem, and 16 imipenem). Of the cases with empirical cefepime therapy, 14 causative isolates were *in vitro* resistant to cefepime, which was therefore regarded as inappropriate empirical therapy, and all later received definitive carbapenem therapy. The 30-day mortality rate of those empirically treated with cefepime (13/53, 24.5%) was similar to the rate of those treated with a carbapenem (25.8%, 8/31; $P = 1.0$) (Fig. 3). Even if only cefepime-susceptible and cefepime-SDD isolates were considered, the 30-day mortality rates were similar in those receiving appropriate empirical cefepime and carbapenem therapy (28.2% [11/39] versus 25.8% [8/31]; $P = 1.0$). In the Cox regression model, empirical cefepime treatment at a high dose (2 g every 8 h) was independently associated with a lower 30-day mortality rate (hazard ratio [HR], 0.12; 95% confidence interval [CI], 0.16 to 0.97; $P = 0.047$) after adjusting for a critical illness (i.e., a Pitt bacteremia score of ≥4), a rapidly fatal underlying disease, and the cefepime susceptibility category. However, in the SDD subgroup of 15 cases, empirical therapy with a high dose (2 g every 8 h) resulted in a better, though not statistically significant, outcome (22.9%, 2/9) than did other dosages (66.7%, 4/6; $P = 0.14$).

Definitive therapy. Of 144 patients with definitive therapy, all were infected by an organism susceptible or SDD to their respective drug and received appropriate doses. Seventy-two patients treated with cefepime for bloodstream infection due to cefepime-susceptible ($n = 56$) and SDD ($n = 16$) isolates were compared with 72 patients with bacteremia due to carbapenem-susceptible isolates treated with a carbapenem (43 imipenem, 28 meropenem, and 1 ertapenem). There were no significant differences in terms of age, sex, comorbidity, source of bacteremia, disease severity, or 30-day mortality rate among those definitively treated with cefepime and a carbapenem (Table 1). A multivariate regression analysis revealed that the presence of a critical illness with a Pitt bacteremia score of ≥4 (adjusted HR [aHR], 12.23; 95% CI, 4.4 to 34.0; $P < 0.001$) and a rapidly fatal underlying disease (aHR, 6.8; 95% CI, 2.1 to 22.3; $P = 0.002$) was independently associated with 30-day mortality.

Of 72 patients with definitive cefepime therapy, 19 (26.4%) died within 30 days. The 30-day mortality rate of those infected by cefepime-susceptible isolates was significantly lower than that of patients infected by cefepime-SDD isolates (16.1% [9/56] versus 62.5% [10/16]; $P < 0.001$) but similar to that of 72 patients with definitive carbapenem therapy (16.1% [9/56] versus 22.2% [16/72]; $P = 0.50$) (Fig. 3). Those infected by ESBL producers had a higher 30-day mortality rate than those infected by the isolates without ESBL (40.0% [16/40] versus 9.4% [3/32]; $P = 0.006$).

In the multivariate analysis, the presence of critical illness (HR, 4.40; 95% CI, 1.02 to 18.89; $P = 0.04$), rapidly fatal underlying disease (HR, 11.27; 95% CI, 1.72 to 73.94; $P = 0.01$), ESBL producers (HR, 12.34; 95% CI, 2.10 to 72.56; $P = 0.005$), and cefepime-SDD isolates (HR, 18.04; 95% CI, 2.66 to 122.18; $P = 0.003$) was independently associated with 30-day mortality, and in contrast, high-dose definitive cefepime therapy was not related to a better outcome (Table 2). Of 19 fatal cases, 16 (84.2%) acquired ESBL-producer bacteremia, and 10 (52.6%) isolates belonged to the SDD category. In the patients acquiring cefepime-SDD isolates definitively treated with cefepime, the Kaplan-Meier survival analysis revealed a worse outcome than in other subgroups ($P = 0.002$, by the log rank test) (Fig. 4). The hazard ratio of 30-day mortality of individuals with definitive cefepime therapy for infections caused by cefepime-SDD isolates was 5.55 (95% CI, 2.12 to 14.53; $P < 0.001$) if compared with that of patients infected by cefepime-susceptible isolates and 2.62 (95% CI, 1.16 to 5.91; $P = 0.02$) if compared with those treated with carbapenem in the Cox regression model after adjustment of confounding variables.

Bloodstream infections due to cefepime-SDD isolates. Overall, 33 patients were infected by cefepime-SDD isolates. Those with empirical cefepime therapy had a higher 30-day mortality

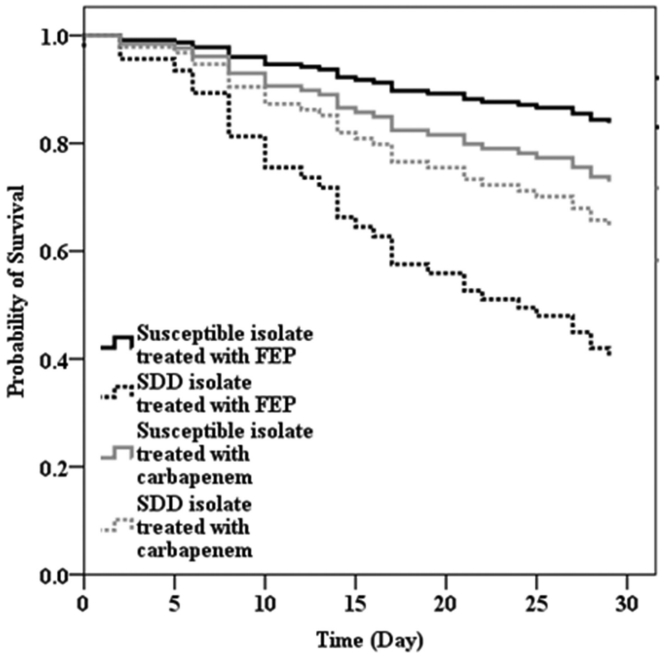

FIG 4 Kaplan-Meier survival curves for the patients with bloodstream infections caused by cefepime-susceptible isolates (MIC, ≤2 μg/ml; solid line) or cefepime-susceptible dose-dependent (SDD; MIC, 4 to 8 μg/ml) *Enterobacter cloacae* isolates definitively treated with cefepime (FEP; black solid line and black broken line, respectively) or carbapenem (gray solid line and gray broken line, respectively) ($P = 0.002$ by the log rank test).

rate than those with empirical carbapenem therapy (71.4% [5/7] versus 18.2% [2/11]; $P = 0.045$). Likewise, those with definitive cefepime therapy tended to have a worse outcome than those with definitive carbapenem therapy (62.5% [10/16] versus 33.3% [4/12]; $P = 0.25$). The 30-day mortality rates were not different among three cefepime dose regimens (i.e., 1 g every 8 h, 2 g every 12 h, and 2 g every 8 h) for cefepime-susceptible or cefepime-SDD isolates (Fig. 5A).

Of 16 patients definitively treated with cefepime, ESBL producers were associated with a higher mortality rate than non-ESBL-producing isolates (100.0% [10/10] versus 0% [0/6]; $P < 0.001$). However, if they received carbapenem therapy, their prognosis was better than that with cefepime therapy (42.9% [3/7] versus 100% [10/10]; $P = 0.015$) (Fig. 5B). Among the cefepime-SDD isolates without ESBL, the outcomes were similar in those with definitive cefepime and carbapenem therapy (0% [0/6] versus 20% [1/5]; $P = 0.46$).

DISCUSSION

This study reported clinical outcomes of adults with *E. cloacae* bloodstream infections in a medical center where cefepime was frequently used as empirical or definitive treatment. Using the clinical outcome of those treated with a carbapenem as the comparator, empirical cefepime therapy heralds a similar prognosis and a high-dose cefepime regimen (2 g every 8 h) is independently associated with a better outcome than other dosages, in accordance with a recent prospective observational study (20). Moreover, clinical outcomes were similar among those definitively treated with cefepime and those definitively treated with a carbapenem at the dosages recommended by the CLSI (16). However, most importantly, we found that among those with definitive cefepime therapy, infection due to cefepime-SDD isolates is an independent risk factor of 30-day mortality. Such a finding will raise the clinical question of cefepime therapy for bloodstream infections due to cefepime-SDD isolates. The recently proposed susceptibility category of SDD for cefepime, initially based on the *in vitro* susceptibility profile, pharmacodynamic/pharmacokinetic data, and limited clinical experience of *Escherichia coli* or *Klebsiella pneumoniae* infections (15, 21), raises more concerns for the adoption of cefepime SDD and dosing issues in a MIC-based therapeutic approach in terms of patient safety.

Several clinical studies supported the idea that cefepime is a reasonable option for invasive *Enterobacter* infections, particularly when the local prevalence of ESBL production is low (1, 9, 10). Recent susceptible breakpoint decreases for cefepime and the lack of need for ESBL detection in *Enterobacteriaceae* pathogens promote clinical use of cefepime at different dosages, based on MIC values (16). However, we found that among the cases of *E. cloacae* bloodstream infections with appropriate definitive cefepime therapy (i.e., those infected by cefepime-susceptible and cefepime-SDD isolates), ESBL production was independently as-

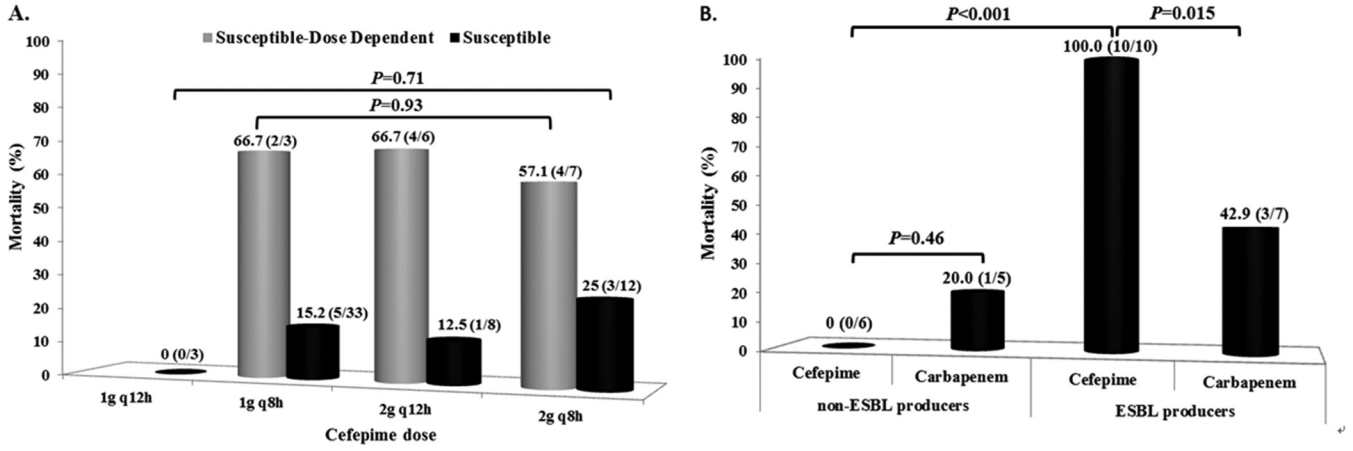

FIG 5 Thirty-day mortality rates of patients acquiring monomicrobial bacteremia due to cefepime-susceptible dose-dependent (MIC, 4 to 8 μg/ml) isolates, categorized by therapeutic dosage of cefepime (A) or ESBL production in those with definitive cefepime or carbapenem therapy (B).

sociated with a fatal outcome. In addition, even among cefepime-susceptible *E. cloacae* isolates, more than 40% exhibited the ESBL production phenotype. Both findings highlight the prognostic significance of ESBL production for *E. cloacae* isolates with a cefepime MIC of ≤8 μg/ml and suggest the reconsideration of ESBL detection, especially at least for *E. cloacae* pathogens.

Another question of clinical interest is that the recommended dosages of cefepime for *Enterobacteriaceae* infections vary with MICs, in order to obtain optimal drug target attainment and possibly better clinical outcomes (15). Moreover, a high-dose regimen of empirical cefepime therapy has been associated with a better prognosis in the cases of bloodstream infections due to a variety of Gram-negative bacilli, and such a therapeutic benefit persists in the isolates with low cefepime MICs (≤0.25 μg/ml) (20). Our data for empirical cefepime therapy for monomicrobial *E. cloacae* bacteremia support the dose-dependent effect. However, with clinical concerns about cefepime-SDD, cefepime-resistant, or ESBL-producing isolates, high-dose cefepime is not the optimal choice for the empirical therapy of suspected *E. cloacae* bacteremia.

The strength of our study was the presentation of both microbiological and clinical outcomes, augmenting the clinical validity of our findings. However, some limitations should be considered in this study. First, this is a retrospective observational study and can be confounded by unmeasured variables. Moreover, multivariate logistic regression analysis is applied to adjust for confounding clinical variables. Second, because only clinical data regarding the hospitalization period were available, we analyzed the in-hospital outcome. It remains undefined whether there is any difference in long-term outcomes between definitive cefepime and carbapenem therapy groups.

In conclusion, cefepime at the recommended doses can be suggested as one of the carbapenem-sparing regimens for definitive therapy of cefepime-susceptible *E. cloacae* infections. Cefepime should be used cautiously for cefepime-SDD *E. cloacae* infections in terms of therapeutic efficacy, since cefepime is becoming inefficient in dealing with *E. cloacae* isolates for which the MIC is higher than 2 μg/ml.

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